Neoadjuvant Chemoradiotherapy Treatment for a Classic Biphasic Pulmonary Blastoma with High PD-L1 Expression

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Abstract. *Pulmonary blastomas are rare malignant tumors, comprising only 0.25-0.5% of all malignant lung neoplasms. The prognosis of pulmonary blastoma is very poor, with an overall five-year survival of 16%. No standard treatment has been defined for unresectable disease. We present the case of a 25-year-old woman with unresectable locally advanced classic biphasic pulmonary blastoma (CBPB) successfully treated with neodjuvant chemoradiotherapy based on two chemotherapy induction cycles of cisplatin plus etoposide, followed by concurrent weekly cisplatin to 50.4 Gy radiotherapy treatment. The patient had a significant reduction in tumor size, allowing for complete resection by pneumonectomy. Molecular study for epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK), proto-oncogene receptor tyrosine kinase (ROS1) and rearranged during transfection (RET) rearrangements, and programmed death ligand 1 (PD-L1) expression was performed in the pre-treatment tumor sample. Our patient presented a high expression (>90% of tumor cells) of PD-L1. To our knowledge, this is the first report of PD-L1 expression in CBPB. This could lead to new treatment options based on new immunotherapy agents blocking the PD-1/PD-L1 pathway for this rare disease with poor prognosis.*

Classic biphasic pulmonary blastoma (CBPB) is a malignant tumor composed of a primitive mesenchymal and epithelial component resembling the fetal lung (1). CBPB is considered a rare subtype of sarcomatoid carcinoma, accounting for about 0.25%-0.5% of all pulmonary malignancies (2, 3). It was first described in 1952 by Barret and Barnard and termed 'embryoma'. In 1961 it was re-categorized by Spencer as pulmonary blastoma (4, 5). Peak incidence is around 35-40 years of age. Apart from complete surgical resection when possible, treatment options for CBPB are limited. Because of the rarity of the tumor type, no standard therapy has been established, although use of radiation and chemotherapy have been sporadically reported (5, 6). Due its rarity, little is known about oncogenic driver mutations that might lead to new treatment options for this disease.

Herein we report the case of an unresectable CBPB managed by neoadjuvant chemoradiotherapy treatment. The tumor was also screened for potential molecular alterations that may offer the possibility of therapeutic options already approved or in development for non-small cell lung cancer

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Key Words: Pulmonary blastoma, neoadjuvant treatment, *EGFR* mutation, PD-L1 expression, ALK-EML4 translocation, chemo-radiotherapy, pembrolizumab.

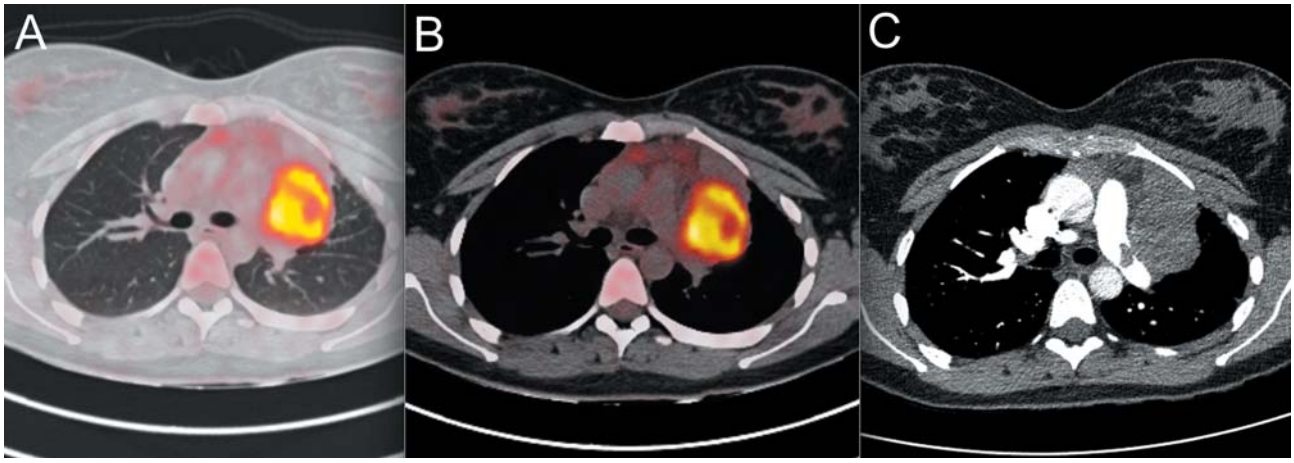

Figure 1. *A, B: Positron-emission tomography with computed tomography scan (PET-CT) pulmonary and mediastinal window. Hypermetabolic parahilar mass of 45×55×52 mm (standard uptake value (SUV)max 20.2) with an image of doubtful left pulmonary artery infiltration and soft thrombus. C: Computed tomographic scan of the pulmonary artery. Parahilar mass with left pulmonary artery infiltration and nodular intraluminal protrusion.*

(NSCLC). To our knowledge, this is the first case of CBPB with high expression of programmed death ligand 1 (PD-L1).

Case Report

A 25-year-old woman, with history of tobacco use (cumulative, four packs/year) and without other previous medical history, presented with cough and hemoptysis. Chest radiographs revealed a well-defined mass in the left upper lobe. Bronchoscopy showed regular bronchial thickening at the left upper lobe. Biopsies were negative for malignancy. Tumor biopsy guided by computed tomographic (CT) scan revealed CBPB. Positron-emission tomography (PET)-CT scan confirmed the known left hypermetabolic parahilar mass of 45×55×52 mm [standard uptake value $(SUV)_{max}$ 20.2] with an image of doubtful left pulmonary artery infiltration and soft thrombus (no intraluminal activity) without lymph node staging T4N0M0 (Figure 1).

The patient was initially discounted as a candidate for surgery and neoadjuvant chemoradiotherapy initiated. We started treatment with two induction cycles based on cisplatin (75 mg/m^2 on day 1) and etoposide (100 mg/m^2 on days 1-3) every three weeks. During induction chemotherapy, 3D radiotherapy planning was calculated, allowing the patient to start concurrent chemoradiotherapy with a total dose of 50.4 Gy in 1.8 Gy daily fractions and five cycles of weekly cisplatin at 40 mg/m^2. The patient tolerated treatment well, with alopecia being the only notable side-effect and without esophagitis, nausea or vomiting.

A PET-CT scan was performed two weeks after finishing radiotherapy in order not to delay surgical treatment and thus avoid surgical complications resulting from radiotherapy-induced fibrosis. PET-CT scan showed a significant radiological and metabolic partial response (SUV_{max} decrease of 68%) (Figure 2) and, most interestingly, the tumor was then considered to be resectable. A left pneumonectomy was performed four weeks after finishing radiotherapy treatment, without postoperative surgical complications. Pathological examination revealed residual pulmonary blastoma with significantly extended areas of necrosis and fibrosis (90% pathological regression). Surgical margins were negative and there was no evidence of regional lymph node involvement (10 negative lymph nodes were analyzed).

Molecular study was performed on the pre-treatment tumor sample. Initially we explored activating mutations of epidermal growth factor receptor (*EGFR*) by polymerase chain reaction for exons 18-21. Due to no detection of mutations in *EGFR*, analysis of rearrangements in anaplastic lymphoma kinase (*ALK*), proto-oncogene receptor tyrosine kinase (*ROS1*) and rearranged during transfection (*RET*) were performed by fluorescence in situ hybridization, with negative results. Finally, we performed an immunohistochemical analysis for PD-L1. Interestingly, the tumor presented high PD-L1 expression with strong intensity (grade 3) according to an intensity scale from 0 to 3 (where 0=no staining, 1=weak, 2=moderate, and 3=strong staining), in 90% of tumor cells (Figure 3). The patient is currently in follow-up with no evidence of recurrence eight months after surgery.

Discussion

Pulmonary blastoma is an uncommon malignancy classified as a rare variant of lung sarcomatoid carcinoma. The World Health Organization subdivided pulmonary blastoma into

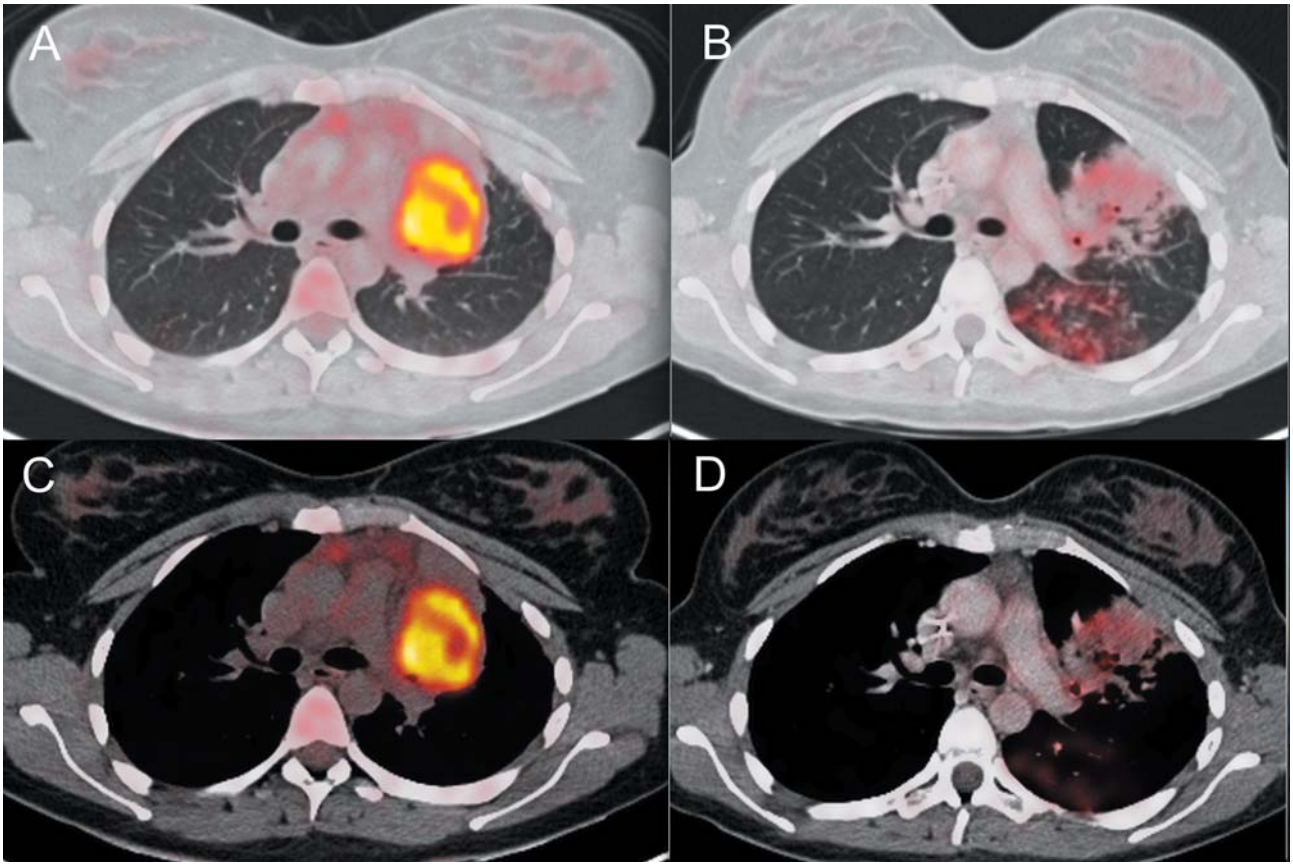

Figure 2. *Positron-emission tomography with computed tomography scan (PET-CT) pulmonary and mediastinal window. A, C. Pretreatment scan; B, D: Post-treatment scan. Significant radiological and metabolic partial mass response. Disappearance of the intraluminal image.*

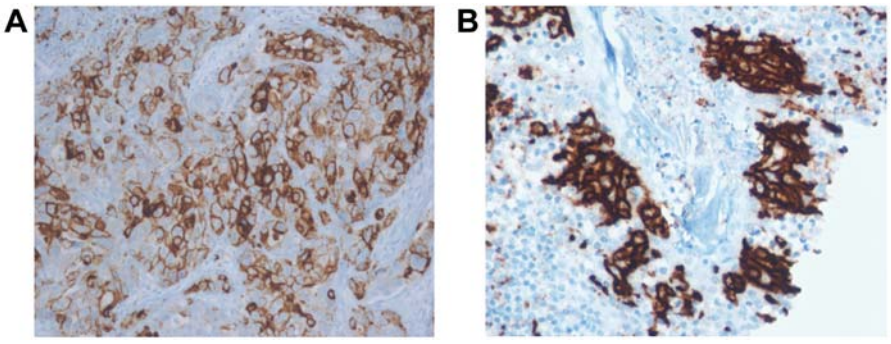

Figure 3*: Programmed death ligand 1 (PD-L1) by immunohistochemistry: PD-L1 staining of representative pulmonary blastoma sample (A). A tonsil section as positive-control was included in the staining run (B). Strong staining can be seen in tissue with PD-L1 (SP142) rabbit monoclonal immunohistochemistry antibody. Images were taken at ×200.*

three categories: well-differentiated fetal adenocarcinoma, pleuropulmonary blastoma and CBPB (5).

CBPB symptoms usually include cough, hemoptysis, chest pain and dyspnea. It presents as a unilateral, large, well-defined lesion on chest x-rays. Microscopically, the tumor simulates a first trimester fetal lung, with malignant epithelial and stromal cells.

Poor prognosis has been described and multidisciplinary treatment is recommended (7). Surgery is the standard treatment for localized disease and there are no guidelines

for unresectable disease. CBPB has a recurrence rate of 43% and a propensity for metastasizing to the brain, mediastinum, pleura, diaphragm, liver, heart, and soft tissues of the extremities (5). Disease recurrence seems to occur during the first 12 months after diagnosis, with the gross size of the tumor (>5 cm) being an adverse prognostic factor (8).

Single radiation therapy has induced objective response in a few cases and local control and palliation of metastases has been achieved by radiotherapy combined with chemotherapy (9). The optimal combination of chemotherapeutics remains to be determined. The overall response rate to first-line chemotherapy without radiotherapy is 26% (8). The evidence available recommends the combination of multiple drugs, and preferred regimens should contain alkylating agents, antibiotics or anti-mitotic agents. Based on a review of all cases published between 1982 and 1994, adjuvant radiotherapy and chemotherapy with cisplatin and etoposide seems to be an effective post-surgery regimen (10).

For patients with pulmonary blastoma who initially present with locally advanced unresectable disease, neoadjuvant chemoradiotherapy treatment should be considered. A previous report of neoadjuvant chemoradiotherapy for unresectable CBPB observed clinical response which made surgery possible. In the case described by Zagar *et al*. in 2010, the tumor was treated with a total dose of 50 Gy in daily fractions of 2 Gy and the patient received two cycles of cisplatin (50 mg/m^2 on days 1 and 8) and etoposide (50 mg/m^2 on days 1-5) during weeks 1 and 5 of radiotherapy (11).

Efforts have been made to define the molecular profile of CBPB. In 2011, Macher-Goeppinger *et al*. described an activating exon 19 *EGFR* mutation in a patient with CBPB (1). We screened our patient's tumor for *EGFR* mutations, and *EML4-ALK, ROS1* and *RET* translocations were explored by fluorescence in situ hybridization, with negative results.

A new treatment approach based on immunotherapy agents is currently being explored for lung cancer. Agents targeting PD-1 and its ligand (PD-L1) are showing promising results in NSCLC: recently, PD-L1 expression was identified in 19% patients who lacked any other targetable alterations (*EGFR, ALK,* or *ROS1*) (12). PD-L1 expression by immunohistochemistry has been significantly associated with adenocarcinoma histology and with the presence of *EGFR* mutations (13). Interestingly, in *EGFR*-mutated tumors, expression of PD-L1 was related with higher response rate, time to progression and survival. In non molecularly selected cancer, tumor cell PD-L1 expression correlates with objective response to anti-PD-1 therapy (39% *vs*. 6%, p=0.025) (14). Recently, the KEYNOTE-001 phase I trial with pembrolizumab (a monoclonal antibody to PD-1) in NSCLC observed that higher expression of PD-L1 is related to better overall response (15). In this study, patients with strong PD-L1 positive staining (≥50% of tumor cells) presented an overall response rate of 37%, whilst for patients with weak staining (1-49% of tumor cells) or without PD-L1 expression there was response in only 15% and 7%, respectively. Therefore, CBPB should be tested for PD-L1 expression as this could provide new treatment options for this rare disease. This is especially interesting considering no objective responses have been described in clinical series of patients who received chemotherapy as a second-line treatment (8).

Conclusion

As far as we are aware of, this is the first case of CBPB tested for expression of PD-L1, showing a very intense positive result (high intensity in >90% tumor cells) concomitant with an absence of *EGFR* mutations and *ALK*, *ROS1* and *RET* rearrangements. This finding could lead to new treatment options based on new immunotherapy agents blocking the PD-1/PD-L1 pathway for this rare disease with poor prognosis.

Conflicts of Interest

None of the Authors has any conflict of interest with regard to this study.

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